The assessment and presentation of Autism Spectrum Disorder and associated characteristics in individuals with severe intellectual disability and genetic syndromes

Moss, Joanna; Howlin, Patricia; Oliver, C

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Jo Moss, Patricia Howlin and Chris Oliver

Cerebra Centre for Neurodevelopmental Disorders,
School of Psychology,
University of Birmingham

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The assessment and presentation of Autism Spectrum Disorder and associated characteristics in individuals with severe intellectual disability and genetic syndromes.

Introduction:

Autism Spectrum Disorders (ASDs[1]) are classified by DSM-IV-TR (APA, 2000) and ICD-10 (WHO, 1992) as pervasive developmental disorders (PDD) characterised by the presence of three core features: qualitative impairments in communication and social interaction and the presence of repetitive behavior and restricted interests. ASDs occur in up to 1% of children in the general population (Baird et al., 2006) and in up to 40% of individuals with severe to profound levels of intellectual disability (La Malfa, Lassi, Bertelli, Salvini, and Placidi, 2004).

Advances in the identification of genetic abnormalities have promoted research into the association between ASDs and ASD characteristics and specific genetic abnormalities that are associated with intellectual disability[2]. The presence of ASD or autistic like characteristics has been reported in a growing list of such genetically determined syndromes including Tuberous Sclerosis Complex, Fragile X, Down, Angelman, Coffin-Lowry, Cohen, Rett, Cornelia de Lange, and Williams syndromes (see Fombonne, 1999; Gillberg & Coleman, 2000 for reviews). The apparent association between genetically determined syndromes and ASD symptomatology clearly has important implications. At the level of aetiology it has been suggested that the study of genetic syndromes may be influential in identifying and understanding genetic and neural pathways underlying ASD (Persico & Bourgeron, 2006). With regard to phenomenology, atypical or unusual profiles of ASD symptomatology have been identified in a number of genetic syndromes including Rett, Fragile X and Cornelia de Lange syndromes (see Cornish, Turk & Hagerman, 2008; Moss, Oliver, Berg, Kaur & Cornish 2008; Mount, Charman, Hastings, Reilly & Cass., 2003; Mount, Hastings, Reilly, Cass & Charman, 2003), leading to considerable debate regarding the boundaries of the autism spectrum. However, the strength of association between ASD and genetically determined syndromes is unclear and detailed study of ASD symptomatology has stimulated discussion about the identification, assessment and nature of ASD characteristics. This debate, alongside the broader issue of the role that degree of intellectual disability might play in the development, manifestation and identification of ASD and associated characteristics, will be highlighted in this chapter. We will consider the prevalence and nature of ASD and associated symptomatology in the intellectual

[1] For the purposes of this review the term Autism Spectrum Disorder (ASD) will be employed throughout the text to refer to all conditions classified by the DSM-IV-TR (2000) within the category of Pervasive Developmental Disorder with the exception of Rett syndrome and Child Disintegrative Disorder. When referring to particular studies, the terminology used by the authors of the study will be employed.

[2] Throughout this chapter we will use the terms 'genetically determined syndromes' or 'genetic syndromes' to refer to conditions that are associated with intellectual disability in which specific genetic aetiology has been identified.

disability population, with particular focus on three genetically determined syndromes; Fragile X syndrome, Tuberous Sclerosis Complex and Rett syndrome, which have received particular attention with respect to their association with ASD. Other syndrome groups that have illustrated particular issues relevant to the syndrome-ASD association and the role of intellectual disability will also be discussed. These include Angelman, Down, Cornelia de Lange and CHARGE syndromes, and Phenylketonuria.[3]

Prevalence of autism spectrum disorder and associated characteristics in individuals with intellectual disability and genetic syndromes:

Prevalence of autism spectrum disorder in individuals with intellectual disability:

Prevalence studies of ASD in individuals with intellectual disability inevitably produce variable estimates because of differences in diagnostic criteria and assessments across the different studies. Deb and Prasad (1994) reported that 14% of individuals aged 5 to 19 years fulfilled DSM-III-R criteria for autism. 35% of those who met criteria had an IQ <35. Using a combination of "expert clinical judgement" and autism specific assessments (Childhood Autism Rating Scale Schopler, Reichller & Renner, 1988; Autism Behavior Checklist Krug, Arick & Almond, 1980), Nordin and Gillberg (1996) reported a rate of 20% meeting criteria for autism or showing autistic like characteristics in individuals with severe intellectual disability (IQ <50) and 5% of individuals with mild intellectual disability (IQ 50 to 70). Similarly, Bradley and Bryson (1998) reported a rate of 25% using the Autism Diagnostic Interview-Revised (Rutter, LeCouteur & Lord., 2003). Higher prevalence rates, of between 30 and 40%, are reported by Rumeau-Roquette, Grandjean, Cans, Du Mazaubrun and Verrier (1997; based on clinical judgement using ICD-9 criteria) and La Malfa et al., . (2004; using the Scale for Pervasive Developmental Disorder in Mentally Retarded Persons; PDD-MRS). Specifically, La Malfa et al. (2004) reported a prevalence rate of 60% in individuals with profound intellectual disability and 37, 24 and 8 % in those with severe, moderate and mild intellectual disability respectively.

Other studies that have addressed the association from the alternative perspective i.e. the prevalence of intellectual disability in individuals with ASD are consistent with findings in the intellectual disability population. Fombonne (2005), estimated that approximately 30% of individuals with ASD scored in the mild to moderate range and 40% in the severe to profound range. Twin studies of

[3] Some of the information in this chapter has been adapted from Moss, Harris & Howlin (in submission).

monozygotic (MZ) and dizygotic (DZ) twins have also confirmed the association between ASD and intellectual disability, demonstrating that more severe intellectual disability is associated with more severe ASD characteristics (see Skuse, 2007).

In summary, ASD is more prevalent in individuals with intellectual disability and a strong, positive correlation between severity of ASD and severity of intellectual disability is well established. This association has raised questions regarding the role of intellectual disability in the development or presentation of ASD. The strength of this association has led some researchers to believe that there may be shared genetic and neurobiological pathways for ASD and intellectual disability (Laumonnier et al., 2007; Abrahams & Gerschwind, 2008). However, in contrast to this, Skuse (2007) suggests that the presence of intellectual disability simply increases the risk that ASD or autistic characteristics will be revealed. Skuse's argument is based around the suggestion that while predisposition to autistic features may be common and independently heritable, level of cognitive ability determines whether or not these characteristics manifest themselves. In this way, lower general intelligence reduces the possibility for cognitive compensation for independently determined ASD traits. Skuse argues that intellectual ability is one of many factors that may influence expression or manifestation of autistic traits.

Autism spectrum disorder in individuals with genetic syndromes associated with intellectual disability:

Rapid advances in technologies for the identification of genetic disorders over the last decade have had a significant impact on research into specific genetic syndromes. In particular, genetically linked disorders associated with intellectual disability have received increasing attention within the literature. This has, in turn, led to the identification of ASD and autistic like characteristics in a growing number of genetic syndromes. Skuse (2007) suggests that this is likely to reflect the associated intellectual disability and other complex cognitive and language impairments associated with particular syndrome groups, however others have suggested that understanding these associations with genetic syndromes may be important to our understanding of genetic or other biological pathways that may lead to the presentation of ASD (Abrahams & Gerschwind, 2008). Three syndrome groups in particular have received attention within the literature regarding their association with ASD characteristics; Fragile X and Rett syndromes and Tuberous Sclerosis Complex

Autism spectrum disorder in Fragile X syndrome:

Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability, occurring in 1 in 3,600 males and 1 in 8,000 females (see Cornish et al., 2008). It results from an excess of CGG trinucleotide repeats on the FMR1 (Fragile X Mental Retardation- 1) gene at location Xq27-3 (Verkerk et al.,1991). Degree of disability is within the mild to severe range for males with milder disability more common in females (Cornish et al., 2008).

Reported prevalence rates of ASD in males with FXS vary widely from 0 to 60% (Brown et al., 1986; Bailey, Hatton, Skinner & Mesibov, 2001; Cohen et al.¸1991; Demark, Feldman & Holdman., 2003; Hagerman, Jackson, Levitas, Rimland & Braden., 1986; Hatton et al., 2006; Kau et al., 2004; Levitas et al., 1983; Reiss & Freund, 1990; Sabaratnam, Turk & Vroegop., 2000; Turk & Graham, 1997) although estimates from more recent studies conducted since 2001 are more consistent, ranging from 21% to 50% (Bailey et al., 2001; Cohen et al.¸1991; Demark et al., 2003; Hatton et al., 2006; Kau et al., 2004; Sabaratnam et al., 2003; Turk & Graham, 1997;). The percentage of ASD in females who have FXS is lower, between 1 and 6% (Mazzocco, Baumgardener, Freund, & Reiss, 1997; Hatton et al., 2006). The variability in prevalence estimates among the earlier studies is likely to be accounted for by the different methodologies and diagnostic and participant inclusion criteria employed across studies. In particular, in early studies conducted prior to the identification of the specific FXS gene location in 1991, heterogeneity across participant samples may account for discrepancies with more recent studies. Recent studies report a strong correlation between degree of disability and presence of ASD characteristics in FXS (Demark et al., 2003; Kaufmann et al., 2004; Loesch et al., 2007), although ASD has also been identified in individuals with the pre-mutation FXS with mild cognitive impairments or IQ in the normal range (Hagerman, Ono & Hagerman, 2005).

Severe autism (as measured by the Childhood Autism Rating Scales, Schopler et al., 1988) is relatively rare in FXS (Bailey et al., 2001; Demark et al., 2003) and a milder presentation is more characteristic. However, fine-grained analysis of ASD characteristics has identified specific areas of behavior which may be qualitatively different from those in idiopathic autism. Social anxiety, extreme shyness and gaze avoidance are highly characteristic of FXS, alongside seemingly preserved emotion sensitivity and willingness to interact (Cornish, Turk & Levitas 2007; Hall, de Benardis & Reiss, 2006; Lesniak-Karpiak, Mazzocco & Ross, 2003; Roberts, Weisenfeld, Hatton, Heath, & Kaufmann., 2007; Turk & Cornish, 1998). Furthermore, the gaze avoidance and perseverative speech described in FXS are reported to be unrelated to verbal ability or age (in contrast to the autism population) and are more marked than in autism or ‘non-specific’ intellectual disability (Sudhalter, Cohen, Silverman & Wolfschein, 1990). The developmental trajectory of ASD symptomatology in FXS is also reported to differ from idiopathic autism. According to some

studies, the rate of autism and social avoidance behaviors increases with age in males with full mutation FXS (Hatton et al., 2006; Roberts et al. 2007), while improvements in core symptomatology with age are typically identified in individuals with idiopathic ASD (Charman et al., 2005; Moss, Magiati, Charman & Howlin., 2008)

A similar pattern of findings has emerged with regard to the identification of socio-cognitive characteristics including Theory of Mind (ToM). Although initial studies of individuals with FXS and ASD described deficits in ToM (Cornish et al., 2008) subsequent research has showed that a general information processing and working memory deficit may account for this poor performance in this area rather than a specific ToM deficit (Grant, Apperly & Oliver, 2007). These findings suggest that the subtle differences between ASD and FXS at the level of behavior may also be reflected at the level of social-cognition.

In summary, the findings in FXS suggest that while individuals may score above diagnostic/clinical cut off scores on diagnostic assessments for ASD, the specific profile of behaviors, the quality and nature of impairments and the trajectory of development of these characteristics may not be typical of idiopathic ASD. Rather, a unique, syndrome specific 'signature' of ASD characteristics and impairments may better describe the phenomenology identified (Cornish et al., 2008). These findings highlight the need for conducting fine-grained investigation of ASD phenomenology in genetic syndrome groups that goes beyond basic clinical diagnostic levels.

Autism spectrum disorder in Rett syndrome:

Rett syndrome (RS) is a neurological disorder, predominantly affecting females, it occurs in between 1 in 15,000 to 22,800 live female births and is caused by mutations on the X-linked MECP2 gene (Kozinetz et al., 1993; Amir et al., 1999). In the classic form of RS, development usually appears typical for the first six to eighteen months, after which a period of regression occurs resulting in a reduction in head circumference growth, onset of seizures, characteristic hand movements and loss of language and motor skills leading to severe or profound intellectual and physical disabilities (Nomura & Segawa, 2005). Some individuals with RS however, retain and develop their language skills further (Kerr, Belichenko, Woodcock & Woodcock, 2001; Smeets et al., 2005). Individuals with the milder form of RS are more likely to be associated with a different genetic mutation of the MECP2 gene (Kerr et al., 2001; Neul et al., 2008; Smeets et al., 2005).

Prevalence figures of ASD in RS range from 25% to 40% and up to 97% in individuals with the preserved speech variant of RS (Mount et al., 2003b; Naidu et al., 1990; Sandberg, Ehlers, Hagberg,

& Gillberg, 2000; Zappella, Gillberg & Ehlers, 1998; Witt-Engerstrom & Gillberg, 1987). The overlap between RS and ASD has previously been considered to be so robust that the syndrome is currently classified as a pervasive developmental disorder (PDD) alongside autism in both the DSM-IV-TR (APA, 2000) and ICD-10 (WHO, 1992) classification systems. This inclusion within the PDD category is now considered by many to be inappropriate (Tsai, 1992), largely due to the fact that there are distinct differences in phenomenology between ASD and RS. For example, many (although not all) individuals with RS develop simple speech prior to regression. Despite the marked deterioration in social skills, eye contact is often maintained and social impairments and autistic characteristics also tend to improve with age after the initial regression (Nomura & Segawa, 2005). Furthermore, the characteristic repetitive hand movements in RS are very different in nature to those observed in individuals with ASD (Howlin, 2002). Even when diagnostic criteria for autism are met, individuals with RS demonstrate an atypical profile of phenomenology, presenting with fewer core features (Mount et al., 2003a). Given the difficulties in indentifying ASD in individuals with severe intellectual disability, the severity of intellectual disability typically found in RS, is likely to further complicate the understanding of the association with ASD. However, studies have identified that the severe degree of intellectual ability cannot solely account for the heightened prevalence of ASD in RS (Mount et al., 2003b, Zappella, Meloni, Longo, Hayek & Renieri, 2001; Zappella et al., 1998).

In summary, the findings of ASD in RS highlight similar conceptual and methodological issues to those raised in FXS. As is the case in FXS, a focus on diagnostic and clinical cut off scores may not be sufficient in order to accurately determine the profile of ASD phenomenology in RS. RS may have a syndrome specific 'signature' of ASD phenomenology that can only be revealed with fine-grained assessment. A further methodological complication for identifying ASD in this group is the profound degree of disability typically associated with the syndrome. It is important to take into account the degree of disability associated with RS and other genetic syndromes associated with severe and profound intellectual disability when assessing and diagnosing ASD in both clinical and research capacities.

Autism spectrum disorder in Tuberous Sclerosis Complex:

Tuberous Sclerosis Complex (TSC) occurs in 1 in 6,000 live births (O'Callaghan, 1999) and is caused by a mutation in the TSC1 (9q34) or TSC2 genes (16p13; Povey et al., 1994). Mutations in either gene result in dysregulated cell development, giving rise to abnormal tissue growth or benign tumours in the brain, skin, kidneys and heart (Crino, Nathanson & Henske, 2006). The TSC phenotype is extremely variable with some individuals having only mild skin problems or mild

seizures; others show severe physical effects and profound intellectual disability (de Vries & Howe, 2007).

Reported rates of ASD in TSC range from 5% to 89% (Baker, Piven & Sato, 1998; Bolton & Griffiths, 1997; Bolton, Park, Higgins, Griffiths & Pickles, 2002; Gillberg, Gillberg & Ahlsen, 1994; Gutierrez, Smalley & Tanguay, 1998; Humphrey, Neville, Clarke & Bolton, 2006; Hunt & Shepherd, 1993; Jambaque et al., 1991; Park & Bolton, 2001; Smalley, Tanguay, Smith & Gutierrez, 1992; Williamson & Bolton, 1995; Webb, Clarke, Fryer & Osborne, 1996;). It has been suggested that comorbidity of ASD in TSC is associated with the presence of temporal-lobe tubers (Bolton et al., 2002). However, it is not the case that *all* individuals with temporal-lobe tubers meet ASD criteria and this association has not yet been replicated (Asano et al., 2001). Few studies have considered the profile of ASD phenomenology in TSC in detail. Smalley et al. (1992) reported that individuals with TSC had somewhat higher (though non-significant) scores than individuals with autism on the social and communication domains of the Autism Diagnostic Interview-Revised (ADI-R; Rutter et al., 2003) and scored significantly lower on the repetitive behavior domain of this measure. Others have reported a global deficit in "play skills" in all children with TSC regardless of ASD status (Jeste, Sahin, Bolton, Ploubidis & Humphrey, 2008). The male: female ratio in TSC is also different to that reported in the ASD population (Smalley, 1998). Such findings suggest that ASD features in TSC may be atypical to those identified in individuals with idiopathic ASD.

While recent studies have identified a greater risk of autism and ASD with increased degree of disability in TSC (de Vries, Hunt & Bolton, 2007; Jeste et al., 2008; Wong, 2006), others have suggested that the ASD-TSC association may be independent of intellectual disability with up to 25% of individuals who meet criteria for autism having an IQ>70 (Harrison & Bolton, 1997; Smalley, 1998). This is notably higher than the prevalence of ASD in the general population, suggesting that degree of disability cannot solely account for the raised prevalence of ASD in TSC.

In summary, Further research is needed in order further delineate the profile of ASD phenomenology in TSC. It remains important for any further studies of ASD in TSC to continue to consider what the role of intellectual disability might be in the ASD-TSC association.

In addition to the increasing interest in the association between ASD and FXS, RS or TSC, there are several other syndrome groups in which identification of ASD characteristics has important clinical

and research issues. These are principally Angelman, Down, Cornelia de Lange, CHARGE and PKU.

Autism spectrum disorder in Angelman syndrome:

Angelman Syndrome (AS) occurs in approximately 1 in 12,000 to 15,000 live births (Clayton-Smith & Pembry, 1992; Kyllerman, 1995) and is caused by maternally inherited anomalies on chromosome 15. Approximately 70% of individuals with AS are due to maternal deletions; between 2 and 5% of cases are caused by paternal uniparental disomy (Robinson et al., 1993). Approximately 2 to 3% of cases have imprinting defects including deletions of the imprinting centre (Saitoh et al., 1997) and a further 1% of individuals have other mutations on chromosome 15 (Chan et al., 1993). The remaining 22-25% of individuals with AS have mutations in the UBE3A critical region (Matsuura et al., 1997). AS is associated with a severe to profound ID (Peters, Beaudit, Madduri & Bacino, 2004), poor mobility and communication skills and seizure disorder (Dykens, Hodapp & Finucane., 2000).

Reported prevalence rates of ASD in AS range from 50% to 81% (Trillingsgaard & Ostergaard, 2004; Peters et al., 2004). Peters et al. (2004) reported that individuals with AS and autism are significantly more intellectually impaired than individuals with AS who do not meet criteria for autism. Bonati et al. (2007) also reported that individuals with AS with better expressive language skills did not meet ASD or autism criteria on the ADOS or ADI-R. It is therefore possible that the identification of ASD in AS may be influenced by the profound disability associated with the syndrome and the overlap in phenomenology that profound disability has with ASD. In line with this, Trillingsgaard and Østergaard (2004) found that individuals with AS and autism were significantly less impaired than individuals with idiopathic autism on items such as social smile, facial expression directed to others, shared enjoyment in interaction, response to name and unusual interests or repetitive behavior, all of which are less reliant on developmental level. These findings suggest that degree of disability in AS may have a significant role to play in the association with ASD and it is less likely to represent a syndrome specific association between AS and ASD. Furthermore, syndrome specific characteristics of AS such as hand flapping and excessive sociability and lack of stranger discrimination may be misrepresented in any autism specific assessment as inappropriate social behavior. Thus, the core features of the syndrome itself may be interpreted as indicators of ASD even though the aetiology of such behaviors may differ. Caution should therefore be taken when assessing and diagnosing ASD in this syndrome group.

With regard to the profile of ASD behaviors in AS, Walz and Benson (2002) and Walz (2007) found that some of the characteristic features of ASD, such as finger/hand flicking, object spinning, lining up objects, looking through people and lack of affection, were rarely reported in AS. This may suggest that even when individuals with AS meet diagnostic criteria for ASD, the profile of behaviors may be somewhat different to that of idiopathic ASD.

In summary, many individuals with AS may meet ASD diagnostic criteria simply because they have not yet reached the developmental level required to demonstrate certain skills and behaviors. Additionally, caution should be taken in using ASD specific assessments that may misidentify syndrome specific characteristics as being ASD like when this may not be appropriate. Any assessment of ASD in individuals with AS should consider these points.

Autism spectrum disorder in Cornelia de Lange syndrome:

Cornelia de Lange syndrome (CdLS) is caused by a deletion in the NIPBL gene on chromosome 5 (locus 5p13) in 20 to 50% of cases (Gillis et al., 2004; Krantz et al., 2004; Miyake et al., 2005; Tonkin, Wang, Lisgo, Bamshad & Strachan, 2004). Additional mutations on the SMC3 gene on chromosome 10 (Deardorff et al., 2007) and X linked SMC1 gene (Musio et al., 2006) are reported to account for 5% of cases. CdLS is characterized by developmental delay, delayed growth, distinctive facial features and limb abnormalities (Jackson, Kline, Barr & Koch, 1993). A number of behavioral characteristics are also considered to be associated with CdLS, including self-injurious and compulsive behaviors, aggression, hyperactivity and an expressive-receptive language discrepancy (Arron et al., 2005; Berney, Ireland & Burn, 1999; Goodban, 1993; Gualtieri, 1991; Hyman, Oliver & Hall, 2002; Oliver, Arron, Sloneem & Hall, 2008).

Early studies of CdLS largely focused on describing self-injurious behavior. However, the association between CdLS and ASD has recently received more attention. Prevalence rates of autism in CdLS range from 50 – 67% (Oliver et al., 2008; Basile, Villa, Selicorni & Molteni, 2007; Berney, et al., 1999; Bhyuian et al., 2006, Moss et al., 2008). Using the Childhood Autism Rating Scale (CARS; Schopler et al., 1988), Oliver et al. (2008) reported that 32.1% of 54 individuals with CdLS scored within the 'severe autism' category of the CARS compared to only 7.1% of a matched control group of individuals with intellectual disability, suggesting that the relationship between CdLS and ASD is not solely accounted for by associated degree of disability. Oliver et al. (2005) also report that those with CdLS scored significantly higher on the Autism Screening Questionnaire

(Berument, Rutter, Lord & Pickles, 1999) than individuals with Cri du Chat and Prader-Willi syndromes, with a mean score comparable to that of a group with Fragile X syndrome.

Fine-grained investigation has indicated that the presentation of the triad of impairments in CdLS may not be typical of that observed in idiopathic ASD. Specifically, social impairment in CdLS may be characterised by selective mutism, extreme shyness and social anxiety (Goodban, 1993; Collis, Oliver & Moss, 2006; Moss et al., 2008). Oliver et al. (2006) also described a high prevalence of socially avoidant behaviors such as 'wriggling out of physical contact' and 'attempting to move away during an interaction' in fourteen out of sixteen individuals with CdLS. These studies indicate that social anxiety and social avoidance may be characteristic of individuals with CdLS and this presentation appears similar to the social anxiety and shyness that is reported in individuals with Fragile X syndrome (see Cornish et al 2008). Further detailed study of early social interaction skills has demonstrated that poor social relatedness may be highly characteristic of CdLS. Poor eye contact in the first year of life has been found to be predictive of social relatedness in later years (Sarimski, 2007). With regard to repetitive behaviors, individuals with CdLS demonstrate a heightened prevalence of compulsive behaviors relative to matched controls with non-specific intellectual disability. Further detailed investigation has revealed that lining up and tidying up behaviors appear to show high levels of specificity in CdLS when compared to six other genetic syndrome groups and individuals with intellectual disability of heterogeneous cause (Moss et al., 2008). As with other areas of the triad of impairments in CdLS, and indeed other genetic syndrome groups, investigation of repetitive behaviors at the subscale level masks these highly specific patterns of behavior, highlighting the need for fine-grained study of behavioral phenomenology. As with FXS, changing profiles of ASD symptom severity and social anxiety in CdLS have been identified as individuals move into late adolescence and adulthood (Collis et al., 2006).

In summary, as with FXS and RS, further detailed investigation at the level of phenomenology has identified a potentially atypical profile of ASD characteristics and impairments in CdLS with social anxiety and selective mutism occurring at unusually high rates and the presence of highly specific repetitive behaviors.

Autism spectrum disorder in Down syndrome:

Down syndrome (DS) is the most common chromosomal cause of intellectual disability, occurring in approximately 10.3 in 10,000 live births (Bell, Rankin & Donaldson, 2003). Typically, DS is caused by the presence of a full or partial trisomy of chromosome 21, although occasionally an

unbalanced translocation involving chromosome 21 has been identified (Dykens et al., 2000). Intellectual disability in DS typically ranges from moderate to severe (Capone et al., 2005).

Previously, the association between ASD and DS was considered to be relatively rare; with the suggestion that DS might be protective against autistic like behaviors (Turk, 1992). However, recent studies have identified prevalence rates ranging from 5 to 39% (Capone et al., 2005; Gillberg et al., 1986; Ghaziuddin, Tsai & Ghaziuddin, 1992; Kent, Evans, Paul & Sharp, 1999; Lowenthal et al., 2007; Lund, 1988; Starr et al., 2005; Turk & Graham, 1997). Difficulties in ToM and emotion perception have also been reported in some children with DS (Barisnikov, Hippolyte & van der Linden, 2008; Wishart, 2007; Wishart, Cebula, Willis, & Pitcairn, 2007; Zelazo et al., 1996). According to Wishart (2007), some of these difficulties cannot be solely accounted for by degree of disability. Interestingly, higher rates of impaired social skills have been reported in family members of individuals with DS and ASD in comparison to individuals with DS without ASD (Lowenthal et al., 2007). Individuals with DS and ASD are reported to have a greater degree of intellectual disability, higher rates of; stereotyped behaviors, hyperactivity and inappropriate speech, compared to individuals with DS but without ASD (Capone et al., 2005). It is not clear how much the increased severity of intellectual disability in this subgroup explains the heightened prevalence of ASD symptomatology.

In summary, Individuals with DS and ASD are reported to have a greater degree of disability, higher rates of stereotyped behaviors, hyperactivity and inappropriate speech compared to individuals with DS who do not have ASD. This suggests that individuals with DS and ASD may form subgroup within the syndrome. However, it is not clear to what extent the greater degree of disability may account for the heightened prevalence of ASD.

Autism spectrum disorder in Phenylketonuria:

Phenylketonuria (PKU) is an inherited defect in protein metabolism, resulting in an inability to break down the amino acid phenylalanine. PKU occurs in approximately 1 in 10,000 live births (Scriver, Eisensmith, Woo, 1994). With early diagnosis and a controlled diet the effects of PKU are minimal. However, late diagnosis and high levels of protein in the diet can produce toxic levels of phenylalanine hydroxylase (PAH) resulting in intellectual disability, seizures and physical abnormalities. Degree of intellectual disability in PKU can range from mild to severe, particularly in late diagnosis cases (although this is not inevitable) but many individuals with PKU have an IQ within the normal range (Yalaz, Vanli, Yilmaz, Tokatli & Anlar, 2006).

With advances in pre/post natal screening and early intervention, the effects of PKU, at least in developed countries, have become far less prevalent. As a result, the association between ASD and PKU is difficult to determine but it is now currently thought that ASD is largely only identified in those individuals with late PKU diagnosis and poorly controlled diet (Baieli , Pavone, Meli, Fiumara & Coleman., 2003). This contrasts with the high rates of associated reported in earlier studies conducted prior to the introduction of improved screening methods (Reiss, Feinstein & Rosenbaum,1986). Overlap in the cognitive profiles of individuals with autism (notably good performance on Block Design and comparatively low scores on Comprehension) and poorly controlled PKU, matched for age and IQ have been reported (Dennis et al., 1999). Individuals with better controlled PKU did not demonstrate this profile. The changes in PKU since the introduction of pre and post natal screening and early intervention presents a natural test of the effects of PAH on cognitive development and importantly development of ASD characteristics.

Autism spectrum disorder in CHARGE syndrome:

CHARGE Syndrome occurs in approximately 1 in 10,000-12,000 live births (Issekutz et al., 2005). The underlying genetic cause has yet to be established although recent studies have identified mutations on the CHD7 gene (Vissers et al., 2004). The acronym, CHARGE, refers to the characteristic physical deficits associated with the syndrome: Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness. However, there is great variability in the presence and severity of these abnormalities. Many children with CHARGE syndrome have IQs in the normal range although intellectual disability can occur.

The prevalence rate of ASD in CHARGE ranges from 15% to 50% (Hartshorne, Grialou & Parker, 2006; Johansson et al., 2006; Smith, Nichols, Issekutz & Blake, 2005). Information is limited regarding the role of intellectual disability and sensory deficits in the development of ASD in the syndrome. Two case studies described by Smith et al. (2005) suggest that ASD is more likely to occur in nonverbal individuals with severe-profound intellectual disability, which might account for their very impaired social skills. However, Hartshorne et al. (2005) reported that the presence of ASD symptomatology in CHARGE could not be wholly accounted for by the visual and hearing impairments typically associated with the syndrome. Further research is needed to identify the role that the associated intellectual disability and sensory impairments may have on the manifestation of ASD characteristics in this group.

Conclusions:

The number of genetic syndromes reported to show an association with ASD is ever growing. The importance of employing a detailed and fine grained assessment of ASD characteristics in genetic syndromes is well illustrated in the examples of Fragile X, Cornelia de Lange and Rett syndromes. Initial descriptions at a superficial behavioral level suggested a significant, even causal, relationship with ASD. However, further detailed investigation of the phenomenology of ASD characteristics within these groups revealed very different developmental, behavioral and cognitive profiles to those found in individuals with idiopathic ASD. It may be helpful to consider these differences as unique and syndrome specific 'signatures' of ASD phenomenology. Further research to consider other syndrome specific 'signatures' of ASD may be important in further our conceptual understanding of the triad of impairments. The fact that the phenomenology of ASD appears to differ across genetic syndromes has particular implications for the debate concerning the boundaries of the autism spectrum. The main question that is raised from this issue is: where does the ever growing number of syndrome groups identified as showing apparently unusual or atypical profiles of ASD sit, conceptually, within the spectrum of autism characteristics?

The complex and often unusual behavioral and cognitive patterns that are characteristic of many genetic syndromes may result in individuals obtaining scores above the autism cut-off on standard assessments even though the underlying neurobiological or cognitive pathways may be different to idiopathic ASD. For example, eye gaze avoidance in FXS and ASD was initially considered to be a shared characteristic in both populations, it is now suggested that in FXS eye gaze avoidance occurs in response to hypersensitivity to sensory stimuli, hyperarousal and social anxiety, while in ASD the same behavior is thought to result from a more general impairment of social interaction (Cornish et al., 2007; Cornish et al., 2008; Hall et al., 2006). Additionally, syndrome specific characteristics such as hand flapping or excessive sociability in Angelman syndrome, can easily be misidentified in autism specific assessments. It is important to be cautious to avoid accepting superficial similarities between syndrome groups and ASD and to look beyond the diagnostic and clinical cut off scores that are so often assumed to be definitive.

The study of ASD in genetic syndromes also raises debate regarding the role of intellectual disability in the presentation of ASD characteristics. According to Skuse (2007) associated intellectual disability in these syndrome groups results in diminished capacity for cognitive compensation of autistic traits, and in this way acts as a risk marker for these characteristics and impairments to be revealed in susceptible individuals. It is clear from our review of RS and CdLS that degree of disability cannot always account fully for the presentation of ASD characteristics,

however there is certainly a need to be extremely cautious when assessing ASD in syndrome groups associated with severe and profound intellectual disability. In Angelman syndrome, Autism specific assessments and indeed diagnostic criteria, may not be sensitive enough to distinguish between ASD related characteristics and the effects of the profound intellectual disability.

Identification and assessment of autism spectrum disorder and associated characteristics in individuals with intellectual disability and genetic syndromes

Distinguishing between autism spectrum phenomenology and the impairments and behaviors associated with intellectual disability (particularly severe intellectual disability) becomes particularly difficult in individuals with genetic syndromes associated with intellectual disability. These individuals often evidence a range of complex cognitive, communicative, behavioral, emotional and physical difficulties that may mask or emulate aspects of ASD or give rise to an atypical presentation of the triad of impairments. From a pragmatic perspective, the aetiology of the behavior presentation is, arguably, unimportant. Rather, it is the ability to accurately assess and identify these shared characteristics and impairments in individuals with intellectual disability that is essential (Moss et al., 2008). Nevertheless, clinical experience and case studies of individuals with genetic syndromes suggest that often differential diagnoses and recognition of ASD symptomatology is not considered or recognised when in fact, it would be beneficial to do so. Diagnostic overshadowing in this population results in many individuals failing to receive or be made aware of educational, behavioral and family support resources that may be helpful. Case studies reported by Howlin Wing & Gould (1995) and Moss, Harris and Howlin (submitted) illustrate how failure to identify ASD characteristics or appropriate recognition of ASD symptomatology can have a significant impact on the individual's behavioral difficulties, mood and quality of life (see Box 1 for example case studies). As a point of caution, while the impact of accurate ASD diagnosis in individuals with intellectual disability and genetic syndromes is clear from these case examples, it is also important not to be over-inclusive of the term ASD (see Box 2 for example case study). Careful investigation in both clinical and research settings taking into account the overlap in phenomenology of ASD, severe and profound intellectual disability, and syndrome specific characteristics and impairments is essential in ensuring that individuals receive appropriate support and education.

Box 1: Case study examples illustrating the implications of recognising ASD in genetic syndromes*:

Jeremy was an 18 year-old with Cornelia de Lange syndrome (CdLS). In his teens he became progressively more withdrawn and uncommunicative and was diagnosed as being selectively mute. However, his eye contact had always been poor and since childhood he had a keen preference for routine and engaged in various repetitive and stereotyped behaviors. The possibility of ASD was not considered until he was 17 years old, despite his parents' previous requests for assessment. The move to college, where the emphasis was on flexibility and student choice, rather than the structure and routine he needed, led to significant deterioration in his mood and behavior. The college were unwilling to modify their programme, insisting that Jeremy needed to 'learn to be more flexible and cope with the changes'. Jeremy became increasingly tearful and withdrawn, stopped taking part in his usual daily activities and refused to go to college. Although he has since received a formal diagnosis of ASD, Jeremy still remains at home, with no educational provision. His outcome contrasts markedly with that of David, another 18 year-old with CdLS for whom, following a period of regression in his late teens, the recognition that he showed many characteristics of ASD, led to his being transferred to specialist autism provision, resulting in significant improvements in his mood and behavior.

Ivan was an 11 year-old boy with Leber's congenital amaurosis, attending a school for visually impaired children. Although he had some very specific areas of skill, especially in music, he showed no interest in other children, had very stereotyped and repetitive language and very fixed routines. The headmaster did not agree with the possibility that he might have ASD and therefore did not support his parents' request for transfer to a specialist ASD unit. Ivan became increasingly isolated, self injurious behaviors increased, and his parents found it more and more difficult to cope. He eventually required placement in a residential school.

Jake was an eight year-old boy with Down syndrome, showed a typical ASD profile of repetitive, non-communicative speech, poor eye contact, limited interaction with other people and a host of repetitive and restricted interests. Although his parents had become increasingly concerned about his lack of progress, school staff interpreted his behaviors as being 'difficult' or 'naughty' and again rejected the possibility of comorbid ASD. Over time, Jake's behavior became steadily more disruptive and aggressive; diagnostic assessment for ASD indicated that he met all the criteria for this disorder and transfer to a specialist autism unit was recommended.

*Please note that while each of the case studies reported here are all individual cases that have been observed/assessed by the authors in clinical or research settings, all cases are reported using pseudonyms.

Box 2: Case study illustrating the implications for inappropriate application of ASD diagnosis:

Mathew, was a young man with Williams Syndrome who, unusually for this condition, also had profound learning disabilities. His limited communication skills, lack of sociability and highly stereotyped behaviors resulted in his being given the additional diagnosis of ASD, despite the fact that these difficulties were explicable in terms of his very low IQ. His parents, having read about various "cures" for ASD, believed that enrolment in an intensive behavioral autism unit would solve all his difficulties, and were bitterly disappointed when the unit would not accept him because of his severe intellectual impairment.

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For example, the behavior management strategies, educational programming and therapeutic interventions that are effective for individuals with autism and those without may be very different (Howlin, 2000; Jordan, 2001). Identification and recognition of ASD characteristics in individuals with intellectual disability and genetic syndromes may also have implications for the way in which challenging behavior may be perceived by professionals and parents. Thus, the reported 'stubbornness' that is frequently identified by parents, teachers and researchers as a personality trait of individuals with DS may be better understood in individuals with DS and ASD as a strong preference for routine. In other words this is a *behavioral* challenge which can be managed with behavioral methods and strategies. Thus, the correct identification of ASD or, at the very least, recognition that the individual shares characteristics and behaviors with the ASD populations, can be important for parent and professional perceptions and attributions about behavior as well as for developing appropriate behavior management strategies and designing educational curricula (Howlin, 2000).

However, as noted above, the significant overlap between the phenomenology of ASD and the presentation of severe to profound intellectual disability gives rise to many difficulties. Both populations share, to some extent, delayed development in communication, presence of repetitive behaviors and lack of imaginative play skills in addition to impairments of social interaction. Stereotyped behaviors are reported in up to 67% of individuals with intellectual disability (Berkson & Davenport, 1962) and 'compulsive' behavior has been reported to occur in up to 40% (Bodfish et al. 1995). As is the case for individuals with autism, a large proportion of individuals with intellectual disability fail to develop communication skills and those who do are delayed in their development (Vig & Jedrysek, 1999). Development of nonverbal communication to accommodate this delay fails to be achieved in both populations (Lord & Pickles, 1996). It is because these areas of communication rely heavily on developmental level (Volkmar, Lord, Bailey, Schultz & Klin,

2004) that these difficulties are not specific to individuals with autism. Thus, some individuals with intellectual disability may appear to fulfil criteria outlined in DSM-IV-R-TV (APA, 2000) and ICD-10 (WHO, 1992) for ASD, purely because they have not yet reached the developmental level required to acquire these behaviors. The current diagnostic criteria for autism do not take this developmental confound into account.

As is apparent from the discussion above, it is important not to accept superficial similarities between the ASD triad of impairments and the problems in these domains that may be accounted for by other factors. Instead it is imperative, for both theoretical and therapeutic reasons, to exam systematically where the similarities and differences lie.

There are several subtle features that may distinguish ASD symptomatology from deficits that arise purely because of severe intellectual disability. It has been suggested that some specific forms of nonverbal communication are relatively unaffected in individuals with intellectual disability. According to Lord and Paul (1997), individuals with intellectual disability show significantly more appropriate eye gaze and facial expression compared to individuals with ASD. Additionally, while both populations are characterised by delayed language development, Lord and Pickles (1996) report that children with ASD develop fewer words and are less likely to develop phrase speech than individuals with intellectual disability without ASD. Jordan (2001) also suggests that impairments in communication in individuals with intellectual disability without ASD are likely to be caused primarily by difficulties in the acquisition of spoken language. Once effective, alternative means of communication are introduced, such as Makaton signing, objects of reference or picture exchange, individuals are often able to use this alternative communication mode for a number of functions. Thus, they have the motivation to communicate but not necessarily the means to do so. Conversely, individuals with ASD may not develop communication skills that can be generalised outside of specific teaching settings even when alternative modes of communication are introduced (Howlin, Gordon, Pasco, Wade & Charman, 2007). Similarly, the marked discrepancy between expressive language level and communicative intent in verbal children with ASD suggests that communication impairments in individuals with ASD relate to underlying impairments in pragmatics and social-communication and a lack of motivation to communicate, rather than an inability to acquire communicative behaviors per se. This suggestion is supported by the fact that communication in individuals with Autism is focussed on the expression of demands and needs (protoimperatives) rather than the use of socially directed communication (protocdeclaratives; Tager-Flusberg, 2000).

Assessment of ASD in individuals with intellectual disability and genetic syndromes:

Reliable and valid assessment of ASD is an ongoing challenge for clinicians and researchers. Alongside the diagnostic taxonomies, a variety of autism specific assessment tools for screening and diagnosis of ASD have been developed. Each of these assessment tools is designed to be appropriate for individuals in different subgroups. The target age range, severity of ASD and degree of disability is somewhat varied across these measures. Also each assessment tool uses different methods of assessment including observation, interview or informant ratings. Table 1 describes some of these assessment tools, their characteristics, psychometric properties and whether or not they have been used to assess ASD in genetic syndromes. Note that this is not an exhaustive list of available assessments but provides information about the most commonly employed measures.

Table 1: Assessments of autism spectrum disorder: Characteristics and psychometric properties*.

Author	Measure	Format	Child	Adult/Adolescent	SID	Time Taken	Reliability	Validity	Use in genetic syndromes **.
				Checklists/Questionnaires					
Krug *et al.*, 1980	Autism Behavior Checklist (ABC)	Screening questionnaire	Yes	Yes	Yes	10-20 minutes	Inter rater reliability variable for total score. Internal consistency good for total score, poor on subscales	Diagnostic validity poor (Yirmiya *et al.*, 1994). Good concurrent validity with subscales on VABS, moderate concurrent validity with CARS	Yes
Matson *et al.*, 2007	Autism Spectrum Disorders—Diagnosis Scale for Intellectually Disabled Adults (ASD—DA)	Informant questionnaire	No	Yes	Yes	31 items	Item test re-test and inter rater reliability is low to moderate-average Kappa scores of 0.295 and 0.386 inter rater and test retest respectively.	Moderate correlation with DSM-IV-TR and ICD-10 criteria	None identified
Ehlers and Gillberg (1993); Ehlers et al., (1999)	Autism Spectrum Screening Questionnaire	Informant questionnaire	Yes	No	No	Brief (27 items)	Test-retest reliability reported to be good (Posserud et al., 2006)	Cut off score reported to have a specificity of .90 and sensitivity of .62 for parent report and .90 and .70 respectively for teacher reports	None identified

Author	Measure	Format	Child	Adult/Adolescent	SID	Time Taken	Reliability	Validity	Use in genetic syndromes **.
				Checklists/Questionnaires ctd.					
Nylander & Gillberg, 2001	Autistic spectrum disorder in adults screening questionnaire (ASDASQ)	Screening questionnaire	No	Yes	No	Brief (10 items)	Test retest and inter-rater reliability are good (based on % agreement)	No published validity data	None identified
Robins *et al*., 2001	Modified Checklist for Autism in Toddlers (M-CHAT)	Simple screening questionnaire	Infants only	No	Mild ID only	Very brief	Internal reliability adequate for total and item level scores.	Good discriminative validity for distinguishing autism from non-autistic individuals. Robins and Dumont-Mathieu (2006)	None identified
Allison *et al.*, 2008	Quantitative-Checklist for Autism in Toddlers	Informant questionnaire	Yes (<2yrs)	No	No (general population screener)	Brief (25 items)	Test-retest reliability is good.	ASD group scored significantly higher on the Q-CHAT compared to controls.	None identified
Rimland, 1964	Rimland's Diagnostic Checklist for Behavior-Disturbed Children	Questionnaire	Unknown	Unknown	Unknown	Unknown	No published reliability	Discriminative validity has not been achieved despite several attempts.	None identified

Author	Measure	Format	Child	Adult/Adolescent	SID	Time Taken	Reliability	Validity	Use in genetic syndromes **.
				Checklists/Questionnaires ctd.					
Rutter *et al.*, 2003	Social Communication Questionnaire (SCQ; developed from the ASQ)	Screening questionnaire	Yes	Yes	Yes	Brief (40 items)	Good internal consistency	Good concurrent validity with the ADI-R and ADOS (Howlin & Karpf, 2004) Good discriminative validity (Rutter *et al.*, 2003).	Yes
Constantino 2002	Social Responsiveness Scale	Informant Questionnaire	≤ 15 ys	No	No	Brief (65 items)	Test –retest good (.80)	Good concurrent validity with the ADI-R (Constantino *et al.*, 2003)	None identified
Swinkels et al. 2006	The Early Screening of Autistic Traits Questionnaire	Informant questionnaire	Yes (<18months)	No	No	Brief (14 items)	Test re-test reliability is good :r =.80	Good discriminant ability between typically developing children and children with ASD characteristics. May not discriminate well between ASD characteristics and developmental delay.	None identified

Author	Measure	Format	Child	Adult/Adolescent	SID	Time Taken	Reliability	Validity	Use in genetic syndromes **.
				Interviews					
Lord *et al.*, 1994	Autism Diagnostic Interview – Revised (ADIR)	Interview	Yes	Yes	Yes (most valid for mild ID; O'Brien *et al.*, 2001)	90-120 minutes	Reliability high at item level	Good discriminative validity for distinguishing autism from mild intellectual disability.	Yes
Wing *et al.*, 2002	Diagnostic Interview for Social and Communication Disorders (DISCO)	Semi-structured interview	Yes	Yes	Yes	3 hours	Inter-rater and test-retest reliability good	Diagnostic cut-off scores significantly related to clinical diagnoses (Leekham *et al.*, 2002)	Yes
Wing, 1980	Handicaps, Behaviour and Skills (HBS)	Semi-structured interview	Yes	No	Mild-moderate ID only	45 minutes-2hrs	Inter rater reliability is high	Good convergent validity with the VABS (van Berckelaer-Onnes *et al.*, 1993)	Yes
Stone and Hogan, 1993	Parent Interview for Autism (PIA)	Interview	Yes	No	Yes	45 minutes	Test-retest reliability is satisfactory. Internal consistency is adequate.	Concurrent validity with the CARS.	None identified
Kraijer, 1997	Scale for Pervasive Developmental Disorder in Mentally Retarded Persons (PDD-MRS)	Interview	From 2 yrs	Up to 55 yrs	Yes	30-60 minutes	No published reliability	Good sensitivity. Only 9% misdiagnosis compared to clinical ratings using the PDD-MRS	None identified

Author	Measure	Format	Child	Adult/Adolescent	SID	Time Taken	Reliability	Validity	Use in genetic syndromes **.
				Observations					
Lord *et al.*, 2000	Autism Diagnostic Observation Schedule (ADOS)	Structured observations	Yes	Yes	Yes	30 – 45 minutes	Overall reliability good. Reliability for individual items mixed.	Good discriminative validity for distinguishing autism and PDDNOS from non-spectrum disorders.	Yes
Bryson *et al.*, 2007	Autism Observation Scale for Infants	Observational assessment	Yes (6-18 months)	No	No	18 item observation – 20 minutes	Inter-rater reliability good. Test-retest reliability fair to good.	Unknown	None identified
Freeman *et al.*, 1978	Behavior Observation Scale (BOS)	Structured observations	Unknown	Unknown	Yes	Unknown	Inter-rater reliability adequate for 55 out of 67 coded behaviors.	Good discriminative validity for distinguishing autism from intellectual disability	None identified
DiLavore *et al.*, 1995	Pre-Linguistic Autism Diagnostic Observation Schedule (PLADOS)	Semi-structured observations	<6yrs	No	Mild ID only	30 minutes	Reliability good.	Good discriminative validity for distinguishing autism from intellectual disability.	None identified

Author	Measure	Format	Child	Adult/Adolescent	SID	Time Taken	Reliability	Validity	Use in genetic syndromes **.
				Observations ctd.					
Freeman *et al.*, 1986.	Ritvo Freeman Real Life Rating Scale	Observations	Unknown	Unknown	Unknown	Unknown	Satisfactory inter-rater reliability even with non-professional raters Internal consistency is variable.	Unknown	None identified
Stone *et al.*, 2000	Screening Tool for Autism in Two-year olds (STAT)	Observations	Yes	No	Unknown	20 minutes	No published reliability	Correctly classified 100% of children with Autism and 97% of children with other ID.	None identified
				Combined Methods					
Ruttenberg *et al.*, 1966	Behavior Rating Instrument for Autistic and Atypical Children (BRIAAC)	Unknown	Unknown	Unknown	Unknown	Unknown	Inter-rater reliability good. Internal consistency good for all subscales	Comparison of total scores on the BRIAAC to clinical ratings indicated high correlations.	None identified
Schopler *et al*,. 1988	Childhood Autism Rating Scale (CARS)	Observation or questionnaire	Yes	Yes	Yes	30-60 minutes.	Internal consistency high. Inter rater reliability good. Test retest reliability good.	Concurrent validity with clinical ratings is good	Yes

Author	Measure	Format	Child	Adult/Adolescent	SID	Time Taken	Reliability	Validity	Use in genetic syndromes **.
Combined Methods ctd.									
Gilliam *et al.*, 1995	Gilliam Autism Rating Scale (GARS)	Interview/ Questionnaire	Yes	Up to 22 years only	Yes	5-10 minutes	Internal consistency strong	Good concurrent and discriminative validity found initially (Gilliam, 1995). Recent studies indicate that sensitivity is very low (South *et al.*, 2002)	Yes
Adrien *et al.*, 1992	Infant Behavioral Summarized Evaluation (IBSE)	Questionnaire based on observations by professional	Infants only	No	Yes	Brief (29 items)	Global score reliability high. Item reliability good for 31 out of 33 items.	Good discriminative validity for distinguishing autism from intellectual disability and typically developing individuals.	None identified

* Screening assessments of behavior that have subscales relevant to ASD are not included in this table since it was considered that such assessments, which are developed for their scope, contain too few items to provide the depth of information necessary to identify autistic phenomenology in detail. Measures of Asperger's syndrome have also not been included in the table since the focus of this chapter is on ASD in the intellectual disability population.

** Has this assessment been identified by the authors to have been used in studies of individuals with genetic syndromes to identify ASD?

Of the assessments detailed in Table 1, the Modified Checklist for Autism in Toddlers (M-CHAT; Robins, Fein, Barton & Green, 2001), the Pre-linguistic Autism Diagnostic Observation Schedule (DiLavore, Lord & Rutter 1995), the Handicaps, Behaviour and Skills Schedules (Wing, 1980), the Autistic spectrum disorder in adults screening questionnaire (Nylander & Gillberg, 2001), Quantitative-Checklist for Autism in Toddlers (Allison et al., 2008), Social Responsiveness Scale (Constantino, 2002), Autism Observation Scale for Infants (Bryson et al., 2007), Autism Spectrum Screening Questionnaire (Ehlers & Gillberg, 1993; Ehlers, Gillberg & Wing, 1999) and the Early Screening of Autistic Traits Questionnaire (Swinkels et al., 2006) are designed for use with individuals with mild intellectual disability or IQs within the normal range and therefore are not suitable for assessing ASD in individuals with more severe intellectual disability. The M-CHAT (Robins, Fein, Barton & Green, 2001), Infant Behavioral Summarized Evaluation (Adrien et al, 1992), P-LADOS (DiLavore et al., 1995), HBS (Wing, 1982), Parent Interview for Autism (Stone & Hogan, 1993), Rimland's Diagnostic Checklist for Behavior-Disturbed Children (Rimland, 1964) and the Ritvo Freeman Real Life Rating Scale (Freeman et al., 1986) are only designed to assess ASD in children and are therefore not suitable for broader age bands. The fact that the identified assessments of ASD tend to be suitable for individuals with intellectual ability of a particular level i.e. mild vs. severe or age range children vs. adults is a problem for the study of ASD in genetic syndromes. Heterogeneity of intellectual ability across and within genetic syndrome groups and the inclusion of broad age inclusion criteria in research studies, means that it may be difficult to identify one single assessment of ASD that is suitable for assessing ASD across the whole range of ability and ages in a single population. Using ASD assessments that cover a broad range of ability and age would be most suitable for use in these groups.

The Gilliam Autism Rating Scale (GARS; Gilliam, 1995) is designed to assess the symptoms of ASD in children and adults up to the age of 22 years with a range of intellectual disability. It can be administered as either an interview or questionnaire. Internal consistency is reported to be good and inter-rater and test-retest reliability were reported by the authors to be adequate. Good concurrent and discriminative validity were

initially reported (Gilliam, 1995). However, South et al. (2002) have recently indicated that the validity of this measure has been previously over-estimated. South et al. (2002) found the GARS to misclassify 52% of their sample (N =119) as not having ASD or having low likelihood of ASD. Similar findings regarding low sensitivity were reported by Lecavalier (2006) in addition reporting lower levels of inter-rater reliability than had previously been reported in the manual. Overall, these findings suggest that caution should be exercised when using the GARS as a diagnostic tool.

Of the measures that are suitable for assessing ASD in both children *and* adults/adolescents with severe intellectual disability, the Scale for Pervasive Developmental Disorder in Mentally Retarded Persons (Kraijer, 1997) and the Autism Behavior Checklist (ABC; Krug et al., 1980) may not have adequate psychometric properties. The PDD-MRS has been reported to have good discriminative validity, however no reliability data have been reported on this measure (O'Brien, Pearson, Berney & Barnard., 2001). With regard to the ABC, initial reports of reliability and discriminative validity were high (Krug et al., 1980). The advantage of this measure is that it includes different score profiles for different chronological age ranges, therefore accounting for possible changes in the autistic profile with age. This may be particularly helpful for use in syndrome populations given that there may be differences in the developmental trajectory of ASD characteristics in particular syndrome groups. Studies of Fragile X and Cornelia de Lange syndromes have identified such differences although this may not be considered for other syndrome groups. However, the original reliability figures were based on percentage agreement, which does not consider the influence of chance and raters were not blind to clinical diagnosis when discriminative validity was tested (Parks, 1983; Volkmar et al., 1988). Further studies using more stringent measures have indicated that internal consistency is good for total score but poor on subscales. This would make detailed investigation of specific behavioral profiles of ASD characteristics in individual syndrome groups difficult to interpret and would result in having to rely on the broad total score levels which may mask syndrome specific behaviors, profiles and phenomenology. The examples of Fragile X, Rett and Cornelia de Lange syndromes demonstrate that broad scoring criteria may not be sufficient to fully understand the

prevalence and phenomenology of ASD in genetic syndromes. Additionally, inter-rater reliability is poor (O'Brien et al., 2001; Sturmey, Matson & Sevin, 1992; Volkmar et al., 1988) and discriminative validity is low. Whilst these measures are reported to be suitable for use with individuals with severe intellectual disability, their psychometric properties are weak and therefore the information derived from these assessments would need to be interpreted with caution.

Interviews measures appropriate for children and adults with intellectual disability:

The Diagnostic Interview for Social and Communication Disorders (DISCO; Wing, Leekham, Libby, Gould & Larcombe., 2002) was designed to provide a systematic assessment of an individual's clinical history from birth and a description of current behavior. The measure is intended for use in obtaining information regarding ASD or other psychiatric disorders. Inter-rater reliability and discriminant validity according to ICD-10 diagnoses are reported to be good (Wing et al., 2002; Leekham et al., 2002). The DISCO was designed primarily to obtain a clinical history of information in a systematic way rather than as a diagnostic instrument. The DISCO also includes items that cover a range of adaptive and developmental skills including self help skills and visuo-spatial skills which may not be relevant to the diagnosis of ASD in addition to information on other psychiatric disorders and forensic problems. Algorithms for identifying diagnostic categories have been devised to enable the DISCO to also be used for research purposes. While these algorithms allow for use in research, the fact that the DISCO is largely intended for recording clinical history and the length of time it takes to administer this interview suggest that it may be more useful in the clinical setting.

The Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter & LeCouteur, 1994; Rutter et al., 2003) is an informant interview that can be used to diagnose ASD and autism children and adults. Inter-rater and test-retest reliability is reported to be good. Reports of the concurrent validity between the ADI-R and a range of other autism specific assessments including the SCQ, ADOS, CARS and SRS have been good (Bishop & Norbury, 2002; Constantino et al., 2003; Perry 2005) although de Bildt et al. (2004) reported the agreement between the ADI-R and the ADOS to be fair in individuals with

intellectual disability and studies have also reported lower levels of internal consistency than that originally reported by the authors (Saemundsen, Magnussen, Smari & Sigurdardottir, 2003).

Diagnostic validity of the ADI-R is reported to be good. However, the ability of the ADI-R to discriminate between ASD and severe intellectual disability is thought to be somewhat limited (see de Bildt et al., 2004, Charwaska, Klin, Paul & Volkmar, 2007; Gray, 2008; Ventola et al., 2006), although other studies have reported validity and reliability of the ADI-R to be good across all ranges of intellectual ability (de Bildt et al., 2004). These findings suggest that the ADI-R may not be sensitive enough for use in individuals with severe and profound intellectual disability and may be most valid for individuals with mild intellectual disability (O'Brien et al., 2001). The ADI-R should be used cautiously in syndrome groups such as Rett, Angelman and Cornelia de Lange syndromes where degree of disability is typically severe to profound.

Questionnaire measures appropriate for children and adults with severe intellectual disability:

Of the measures reported in Table 1, there is only one questionnaire that is suitable for use in children and adults with severe intellectual disability. The Social Communication Questionnaire (SCQ; Rutter et al., 2003), originally designed as the Autism Screening Questionnaire, (Berument et al., 1999) is a 40-item informant questionnaire that screens for the behaviors and features of communication and social interaction that are associated with autistic spectrum disorder. Items relate to three different domains: reciprocal social interaction, communication and restricted, repetitive and stereotyped patterns of behavior. Two forms of the SCQ have been developed. The lifetime version is completed with reference to the developmental history. The current version is completed with reference to behavior during the most recent three-month period.

The discriminant ability of the SCQ is high in differentiating ASD from non-autism conditions and similarly good for differentiating between autism and intellectual disability. The authors identify a cut off score of 15 as the standard optimal cut off for distinguishing individuals with Pervasive Developmental Disorders (including autism)

from other diagnoses with good sensitivity and specificity for distinguishing individuals with autism from those with intellectual disability. A higher cut off of 22 is reported by the authors to differentiate between individuals with autism and those with other Pervasive Developmental Disorders. The discriminative ability of this higher cut off score for distinguishing autism from intellectual disability is not reported in the manual. The measure has also been shown to have good concurrent validity with the Autism Diagnostic Interview and with the Autism Diagnostic Observation Schedule (Berument et al., 1999; Howlin & Karpf, 2004). Internal consistency is also good (Berument et al., 1999). Validation of the SCQ with younger children has yielded inconsistent findings. Some studies have reported reduced sensitivity and specificity (Eaves et al., 2006a; 2006b; Snow & Lacavalier, 2008) while others have evidenced closer agreement with the original levels of sensitivity and specificity reported by the authors (Chandler et al., 2007). No inter-rater or test-retest reliability data for the SCQ have been reported by the authors.

Importantly individuals who are non-verbal (and therefore likely to have a lower degree of intellectual disability) are not able to score on 7 of the 39 items (18%) in the questionnaire. This scoring disadvantage is not taken into consideration at the level of total or subscale scores. This problem is particularly relevant to Angelman and Cornelia de Lange syndromes and other syndrome groups in which the number of individuals with verbal skills is very limited and makes the use of this measure in cross syndrome comparisons of ASD profiles and prevalence scoring above clinical cut off scores very difficult. One further point of consideration is the fact that the SCQ was developed as a screening instrument and therefore the authors suggest that this assessment should not be used alone to identify and diagnose ASD.

Observational measures appropriate for children and adults with intellectual disability:

Of the measures reported in Table 1, there is only one observational measure that is appropriate for use with children and adults with severe intellectual disability. The Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, Dilavore & Risi, 2000) is

a semi-structured, standardised assessment of communication, social interaction and play or imaginative use of materials. The assessment is suitable for individuals with a range of developmental levels, expressive language skills and chronological ages. The Autism Diagnostic Observation Schedule consists of standardised activities that allow the examiner to observe behaviors that have been identified to be important for the diagnosis of ASD. The assessment incorporates the use of clear, planned social 'presses' which provide the optimum opportunity for the participant to display certain behaviors or responses that are relevant to the diagnosis ASD. The presence/absence and nature of these behaviors and responses are recorded. The assessment consists of four modules, each of which can be administered in 30-45 minutes. Each module has its own protocol. Selection of a particular module is based on the individual's expressive language skills and chronological age.

Good discriminative validity has been established (Lord et al., 2000). While there have been some concerns regarding the discriminative ability of the ADOS in children with severe intellectual disability, diagnostic validity has been reported to be good across a range of ability levels (O'Brien et al., 2001; de Bildt et al., 2004). Concurrent validity with the Autism Diagnostic Interview-Revised has largely been reported to be good although de Bildt et al. (2004) reported only fair agreement with the ADI-R in individuals with intellectual disability. The inconsistency of these findings regarding validity should be borne in mind when using this assessment for both clinical and research purposes. Checking reliability and validity of scoring methods within individual study samples as has been conducted by Moss et al. (2006) in a study of individuals with Cornelia de Lange and Cri du Chat syndromes, may be helpful, particularly in groups associated with more severe degree of disability which are more likely to be affected by these validity and reliability issues.

The observational nature of the ADOS assessment is advantageous and allows for a detailed picture of autistic phenomenology. Importantly, the assessment provides the opportunity to identify some of the more subtle behavioral characteristics of ASD, enabling better differentiation of autistic phenomenology from global intellectual disability. The assessment also provides the opportunity to conduct real time coding of

behavioral characteristics or impairments that can be used to help validate rating information (Moss et al., 2006). However, given that the focus of the ADOS is on current behavior it is suggested by the authors that this assessment should not be used without an accompanying diagnostic interview or screening tool to aid diagnosis and clinical judgement.

Combined measures appropriate for children and adults with severe intellectual disability

The Childhood Autism Rating Scale (CARS; Schopler et al., 1988) assesses the severity of symptoms associated with ASD using a short parent/carer interview and observation method and has been shown to be useful in individuals across the age range. Inter-rater and test retest reliability are good and internal consistency is reported to be high (Perry et al., 2005). Discriminative validity has been reported to be good across a number of studies (Schopler et al., 1988; Perry et al., 2005) and good concurrent validity with the ADI-R has also been demonstrated. The main disadvantage of this instrument is that it does not take developmental level into account when scoring. Given the overlap between ASD and degree of disability, this oversight may have a significant impact on the utility of this measure for individuals with intellectual disability and particularly in those syndrome groups in which severe and profound intellectual disability is typical such as Angelman syndrome. In particular, studies have shown that the CARS may be likely to misdiagnose young children with intellectual disability who do not have ASD. Other studies have identified that this measure may not be sensitive enough to diagnose autism correctly until children reach three years of age (Lord, 1995) and others report that scores on the CARS demonstrate a strong, negative correlation with level of IQ and adaptive level (Perry et al., 2005). Consequently, this assessment may not be suitable for assessing autism in young children or individuals with intellectual disability. The CARS has also been criticised for not being aligned with prevailing diagnostic criteria since it was published in 1988 and therefore based on the DSM-III criteria. However, Perry et al. (2005) note that the CARS does include items that map onto the three core diagnostic areas outlined in the DSM-IV, although it does not include items referring to peer

relationships, joint attention or symbolic play which may be important for early diagnosis. Rellini, Tortolani, Trillo, Carbone and Montecchi (2004) also report a high level of agreement between DSM-IV clinician diagnosis and scores on the CARS although the ability of the CARS to distinguish different subtypes of ASD is limited.

Conclusions:

A number of different assessment tools are available that complement the use of expert clinical judgement for the diagnosis of ASD and which can be used in the assessment of ASD in genetic syndromes associated with intellectual disability. These assessments include a range of formats (questionnaire, interview or observation) and are designed for different purposes (screening vs. diagnosis) and for different age ranges and levels of intellectual ability. However, many were not designed for use with individuals with severe and profound degrees of intellectual disability, others were developed for use with young children only and are therefore not appropriate for use with adolescents or adults. The fact that different measures are more or less suited to particular levels of intellectual disability and age ranges can be problematic for use in syndrome groups in which there may be a range of intellectual ability. Intellectual ability in Tuberous Sclerosis Complex for example ranges from normal to severe. Finding a single measure of ASD that can be used across the board in a single syndrome group is difficult, potentially resulting in having to employ different measures of ASD within a single study population in order to cater for all levels of ability.

Of those that can be used in both children and adults with severe intellectual disability, findings regarding psychometric properties have been somewhat mixed, particularly with regard to their ability to distinguish ASD from severe intellectual disability in young children. Thus, when using ASD assessments in a research capacity, greater attention should be given to consider the validity of the assessment in relation to the specific study sample in which the assessment is being used. This is particularly important when using ASD assessments in syndrome groups such as Angelman syndrome in which the

associated degree of disability (typically profound) makes this population more vulnerable to these issues of validity and reliability.

It is important to remember that standardised assessments are designed to *aid* the clinical diagnosis of ASD; they are not infallible. It is generally considered to be necessary in both clinical and research work to use a combination of assessments in addition to expert clinical judgement in order to accurately identify ASD in any individual regardless of genetic status or degree of disability, although it is clear that even more caution is needed in such groups. Assessment tools like the ADI-R (Rutter et al., 2003) or ADOS (Lord et al., 2000) were developed to distinguish between children with ASD and typically developing children, or children with general ID. They were not designed to distinguish social-communication impairments in genetic syndromes which may be common but may be complex and present ASD profiles and characteristics that are somewhat different in nature, development and aetiology to those that are typical of idiopathic autism. At the broad level of diagnostic/clinical cut off scores, autism specific assessments may not be sensitive enough to identify the very subtle differences in ASD profiles, developmental trajectories that have been identified within the literature in some genetically determined syndromes and any syndrome specific characteristics that may be mis-identified in an autism specific assessment. This requires any assessment of ASD to demonstrate strong reliability and validity at both the subscale *and* item level in order to enable researchers and clinicians to feel confident in their identification of ASD characteristics. For the purpose of considering subtle differences or unusual profiles in genetic syndromes, the use of the ADOS may be preferable as it allows for detailed observation of specific behaviors and characteristics within a standardised setting. In this way, detailed investigation of behaviors in genetic syndromes can go alongside the scoring and rating system that accompanies this assessment. The ADOS provides a standardised setting in which to observe and code real time frequency and duration of core diagnostic characteristics and impairments. This is not only useful for detailing phenomenology of ASD behaviors but also for providing further information about the validity of the assessment in the specific samples being investigated.

General concluding remarks:

In this chapter we have considered the prevalence and phenomenology in individuals with genetic syndromes associated with intellectual disability. It is clear from the case studies presented that accurate identification and recognition of ASD phenomenology in individuals with genetic syndromes is extremely important in ensuring that they receive appropriate educational placement and behavior management strategies. However, research in this area has identified a number of methodological and conceptual issues that may impact on the way in which assessment and diagnosis of ASD in these individuals might be approached. The most prominent difficulty in accurately identifying ASD in these syndrome groups is the overlap between behaviors and impairments accounted for by associated intellectual disability and the behaviors and impairments associated with ASD. This is particularly difficult for individuals with severe to profound intellectual disability. The diagnostic criteria outlined by the DSM-IV-TR (APA; 2000) and ICD-10 (Who, 1992) manuals may not be sensitive enough to distinguish between individuals who have not yet attained the appropriate level of development required to demonstrate a particular skill and those who show a genuine impairment in these skills. The difficulties in accurately recognising and diagnosing ASD characteristics in this population are reflected in the inconsistent psychometric properties of a number of autism specific assessments when used at these levels of ability.

We have highlighted the need to recognise that assessments of ASD were not necessarily designed for use in individuals with genetic syndromes who show a range of complex and often unusual behavioral and cognitive impairments. It is important to be aware of syndrome specific behaviors and be cautious of possible their misidentification in autism specific assessments. Caution is needed in order to avoid accepting superficial similarities or heightened scores on ASD assessments that may be accounted for by other syndrome specific factors.

Finally, we have highlighted the importance of conducting detailed assessment of behavioral phenomenology. Studies in Fragile X, Rett and Cornelia de Lange syndromes

have identified unusual or atypical profiles of ASD phenomenology and differing developmental trajectories of behaviors and impairments which have, in turn, questioned the prevailing conceptualisation of the triad of impairments and highlighted the need to look beyond the level of diagnostic or clinical cut off scores when identifying and assessing ASD characteristics. It is therefore important that assessments of ASD have good item level reliability and validity in addition to good psychometric properties at the domain or subscale level. Detailed and well standardised observational assessments such as the ADOS may be particularly suited to the identification of more subtle social skills and impairments.

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